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## A Comparative Evaluation of Some Ortho Directing Groups for Cubane

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# A Comparative Evaluation of Some Ortho Directing Groups for Cubane

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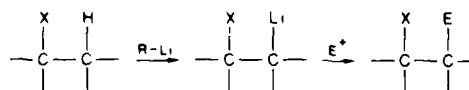
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The "ortho lithiation" technique has been widely used for the regiospecific substitution of electrophilic groups in both aromatic and nonaromatic systems.<sup>1-6</sup> This procedure is based upon the observation that certain functional groups X promote the lithiation of an adjacent ("ortho") carbon, which is then susceptible to electrophilic attack.

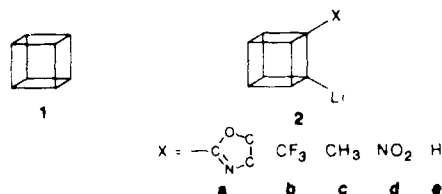


The role of the directing group X is believed to include (a) enhancement of the acidity of the  $\alpha$ -hydrogens, thus promoting its replacement by  $\text{Li}^+$ , and (b) stabilization of the lithiated intermediate, in which the ortho carbon is

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activated toward electrophilic attack by means of an interaction between X and the lithium.<sup>3,5,7</sup> Accordingly, it is anticipated that effective directing groups should be characterized by strong inductive electron-withdrawing tendencies and also by a capacity for coordinating with metals, for example, through lone pairs. Tertiary amide groups, for instance, have been found to be particularly good directing groups.<sup>5-9</sup>

Our objective in this work has been to carry out, by a computational procedure, comparative evaluation of several different functional groups in terms of their abilities to promote ortho substitution on cubane (**1**, a strained polyhedrane system). We have focused particularly upon the ortho-lithiated intermediate that is formed in each case, represented by structure **2a-d**.



The oxazoline and the trifluoromethyl groups (**a** and **b**, respectively) are known to be good directing agents.<sup>3</sup>  $\text{CH}_3$  is not expected to show such activity and is included primarily to serve as a point of reference. It would be particularly interesting if  $\text{NO}_2$  should show signs of being an effective directing group, since this would have important implications for the synthesis of polynitro polyhedranes.

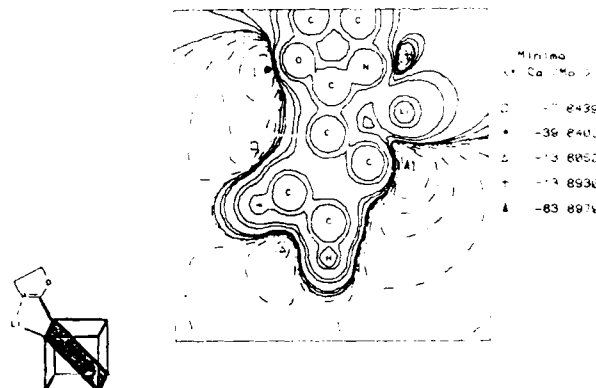
### Methods

We have computed optimized structures for the four molecules **2a-d**, by using an ab initio self consistent field molecular orbital procedure (GAUSSIAN 82).<sup>10</sup> Because of the size of the system being studied, the optimizations were carried out at the STO-3G level. (The structures will be provided for interested readers upon request.) These geometries were used to calculate the STO-5G molecular electrostatic potential of each system in the diagonal plane passing through the two substituted carbons.

The electrostatic potential that is created at any point  $\vec{r}$  in the space around a molecule by its nuclei and electrons is expressed rigorously by eq 1. Where  $Z_A$  is the charge

$$V(\vec{r}) = \sum_A \frac{Z_A}{|\vec{R}_A - \vec{r}|} - \int \frac{\rho(\vec{r}') d\vec{r}'}{|\vec{r} - \vec{r}'|} \quad (1)$$

on nucleus A, located at  $\vec{R}_A$ , and  $\rho(\vec{r})$  is the electronic density function of the molecule, which we obtain computationally. The first term on the right side of eq 1 represents the contribution of the nuclei, while the second gives that of the electrons. Thus an approaching electrophile will tend initially to go to those regions in which  $V(\vec{r})$  is negative, in which the effect of the electrons is dominant, and especially to those points at which  $V(\vec{r})$  reaches its most negative (minimum) values. The electrostatic potential is now widely used in interpreting and predicting molecular reactive properties.<sup>11-13</sup> It is important to note



**Figure 1.** Calculated electrostatic potential of 1-lithio-1-(2-oxazoliny)cubane (**2a**) in a diagonal plane, as shown. Dashed contours correspond to negative potentials; the zero contour is shown. The magnitude of the other contours are in kcal/mol: -50.2, -37.6, -25.1, -12.5, -6.3, -3.1, -0.6, 3.1, 6.3, 31.4, 62.7, 314.0, 627.0. The locations and values of the minima are indicated.

that  $V(\vec{r})$  is a real physical property and can be determined experimentally as well as computationally.<sup>13</sup>

### Results and Discussion

In an earlier study,<sup>7</sup> we presented the electrostatic potential of lithiocubane (**2e**) and pointed out the very unusual feature of a relatively strong negative region (minimum = -38 kcal/mol) associated with a carbon (the one that is lithiated). We showed further that when an amide is present on an adjacent carbon, it interacts with the lithium to stabilize the system. This interaction causes the lithium to shift somewhat toward the amide oxygen; the calculated Li-O separation is 1.80 Å, considerably less than the sum of the lithium and oxygen van der Waals radii, 3.3 Å.<sup>14</sup> As a result, there is created a channel of strongly negative electrostatic potential, with a minimum of -83 kcal/mol, leading to the lithiated carbon. Thus the amide group clearly has the effect of activating the molecule toward electrophilic attack on an ortho carbon. (For a tertiary amide, the channel minimum was -85 kcal/mol.<sup>7</sup>)

Figure 1 shows that the situation in the case of 2-lithio-1-(2-oxazoliny)cubane (**2a**) is very similar to that described above for the amide directing groups. The lithium is shifted toward the oxazoline nitrogen (the Li-N separation is 1.86 Å, with the sum of the van der Waals radii being 3.4 Å),<sup>14</sup> and there is again a strong negative channel leading to the lithiated carbon, with a minimum of -83 kcal/mol. In terms of these factors, then, 2-oxazoline **a** should be a good directing group, as indeed it is known to be.<sup>3</sup>

It is seen in Figure 1 that there are also other negative regions in **2a**, in addition to that associated with the lithiated carbon. These can be attributed to the lone pairs of the oxazoline oxygen and nitrogen and also to the unsubstituted C-C bond. With regard to the latter, we have found that the C-C bonds in strained hydrocarbons in general, and also in some of their derivatives (e.g. **2a**), have negative electrostatic potentials near their midpoints.<sup>15-19</sup>

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**Figure 2.** Calculated electrostatic potential of 2-lithio-1-(trifluoromethyl)cubane (**2b**) in a diagonal plane, as shown. Dashed contours correspond to negative potentials; the zero contour is shown. The magnitude of the other contours are in kcal/mol: -50.2, -37.6, -25.1, -12.5, -6.3, -3.1, -0.6, 3.1, 6.3, 31.4, 62.7, 314.0, 627.0. The locations and values of the minima are indicated.

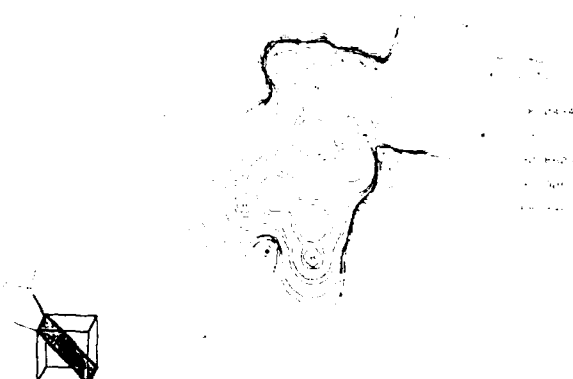


**Figure 3.** Calculated electrostatic potential of 2-lithio-1-methylcubane (**2c**) in a diagonal plane, as shown. Dashed contours correspond to negative potentials; the zero contour is shown. The magnitude of the other contours are in kcal/mol: -12.5, -6.3, -3.1, -0.6, 3.1, 6.3, 31.4, 62.7, 314.0, 627.0. The locations and values of the minima are indicated.

These are fully consistent with the observed reactive behavior of these molecules toward electrophiles.

In the present context, the key feature of Figure 1 is the negative channel to the lithiated carbon. This represents an important aspect of the activation of the ortho carbon by the 2-oxazoline directing group. When the latter is replaced by  $\text{CF}_3$  as the directing agent (structure **2b**), this feature is modified to only a minor extent (Figure 2). The minimum near the ortho carbon is now -78 kcal/mol, which still corresponds to a very significant activation of this position toward electrophilic attack.

In marked contrast is the situation when  $\text{CH}_3$  tries to take on the role of the directing group (**2c**). There is now no shifting of the lithium atom and no strongly negative channel to the ortho carbon (Figure 3); the minimum in



**Figure 4.** Calculated electrostatic potential of 2-lithio-1-nitrocubane (**2d**) in a diagonal plane, as shown. Dashed contours correspond to negative potentials; the zero contour is shown. The magnitude of the other contours are in kcal/mol: -37.6, -25.1, -12.5, -6.3, -3.1, -0.6, 3.1, 6.3, 31.4, 63.0, 314.0, 627.0. The locations and values of the minima are indicated.

that spatial region is now -33 kcal/mol. The picture is very much the same as that obtained earlier for lithiocubane.<sup>7</sup> There is clearly no activation of the ortho position.

Finally, Figure 4 shows the electrostatic potential for 2-lithio-1-nitrocubane (**2d**). There is again an interaction between the two substituents; the lithium is only 1.76 Å from the oxygen, while the sum of the van der Waals radii is 3.3 Å.<sup>14</sup> This produces a channel of negative potential to the lithiated (ortho) carbon, with a minimum of -68 kcal/mol (compared to -38 kcal/mol in that region for lithiocubane, without any second substituent). Thus  $\text{NO}_2$  does definitely activate the ortho position toward electrophilic attack, although not as well as 2-oxazoline and  $\text{CF}_3$ .

### Summary

We have carried out a computational assessment of the relative ortho directing powers of four different functional groups in terms of their tendencies to interact with an adjacent lithium substituent, thereby producing a channel of strongly negative electrostatic potential leading to the lithiated (ortho) carbon. In terms of the factors examined in this analysis, it appears that the nitro group should have at least a moderate ortho-directing capability.

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**Registry No.** **2a**, 111976-24-0; **2b**, 111976-25-1; **2c**, 111976-26-2; **2d**, 111976-27-3;  $\text{CF}_3$ , 2264-21-3;  $\text{NO}_2$ , 10102-44-0;  $\text{CH}_3$ , 2229-07-4; 2-oxazoline, 504-77-8.

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